REMARKS

With entry of this amendment, Claims 27-50 are pending. Claim 27 has been amended. Support for the amendments to the claim can be found on page 7, lines 11-17. Sequence identification numbers corresponding to the previously filed sequence listing have been added on pages 14, 19, 23 and 31. No new matter has been added by these amendments.

Sequence Compliance

The Office Action stated that there were sequences that did not have SEQ ID numbers associated with them. Applicants have amended the specification to include the appropriate SEQ ID numbers. The sequence on page 22 was inadvertently omitted from the sequence listing under 37 C.F.R. §1.821(a)(1) and (a)(2). A substitute sequence listing has been filed. The Examiner is requested to withdraw this objection.

Drawings

The quality of photographs 3 and 7, the margins in figure 1, and the character of the lines, numbers and letters in figures 1, 2 and 8 were objected to by the Draftsperson as not complying with 37 C.F.R. §1.84 or §1.52. Five pages of substitute drawings are submitted herewith.

35 U.S.C. §102(b)

Claims 27-34 are rejected under 35 U.S.C. §102(b) as being anticipated by Blissard *et al.*, U.S. Patent No. 5,750,383 (hereinafter Blissard). The Office Action states "Blissard *et al.* teach [the] use of a novel baculovirus cloning system in which an essential gene for replication is removed from or inactivated from the viral

genome. Cells are transfected with a plasmid that contains the essential gene linked to a foreign gene." Applicants traverse this rejection.

Blissard uses whole virus particles. Virus particles themselves are unstable and break down. This releases DNA into the environment where it is likely to be degraded. Because the system described in Blissard uses whole virus particles, it requires that the cells be infected with virus at a different time or at a different step from when the foreign DNA is transfected. The exemplified system in Blissard also requires a specific insect cell-line comprising a transfected gp64 gene integrated into the host cell to generate virus (see column 4, lines 15-21 and column 5, lines 29-49). The intermediate insect cell containing the transfected gp64 gene rescues the defective virus. This system produces a virus having gp64 in its coat, but lacking the gene to make more gp64. Additionally, the system disclosed by Blissard results in low yields of virus because infection of the insect cell by the virus particles initiates the host cell's protein synthesis and triggers the disintegration of the host cell DNA.

In contrast, the present invention uses the naked DNA of the baculovirus vector. The use of the naked DNA allows the transfection of cells with the baculovirus vector and the foreign DNA simultaneously and does not use an intermediate insect cell to make the viral vector. Accordingly, the present invention is not disclosed, taught or suggested by Blissard. Applicants respectfully assert that the rejection under 35 U.S.C, §102(b) has been overcome and request its withdrawal.

35 U.S.C. §102(e)

Claims 27-32 are rejected under 35 U.S.C. §102(e) as being anticipated by Clark *et al.,* U.S. Patent No. 6,225,060 (hereinafter Clark). The Office Action states " Clark *et al.* teach [the] use of a baculovirus vector for expression of genetic material. As shown in figure two, the method involves cloning of a cDNA of interest by presenting an insect cell with a baculovirus DNA deleted of p-35 and orf-1629 with a

linear DNA comprised of baculovirus DNA and a p-35 gene and a orf-1629 gene. Co-transfection yielded recombinant baculovirus in a process that did not utilize cloning steps." Applicants traverse this rejection.

Applicants assert that Clark discloses a recombinant baculovirus expression system that is not capable of being maintained in an intermediate host. Specifically, Clark discloses the use of a modified baculovirus that lacks a functional p-35 gene. (See Figure 2) The product of the p-35 gene allows the virus to replicate in Sf cells by preventing the cells from undergoing apoptosis. (*See* Clem, R, Flechheimer, M and Miller, L.K. (1991), Prevention of apoptosis by a baculovirus gene during infection of insect cells. *Science* 254, 388-1390, attached.) In the absence of p-35 in the vector disclosed by Clark, the Sf cells undergo apoptosis and the virus cell cannot complete its replication cycle. The only way to replicate the vectors of Clark is to use a cell line in which p-35 is not needed to prevent apoptosis from occurring. In order to replicate the virus using the system described by Clark, a host cell, such as *Trichoplusia ni,* must be used. In using this system, a heterogenous virus population is created prior to any experimentation, rendering the stock of virus unusable for repeat experimentation or as a control. (*See* Fraser, M.J. et al., Acquisition of Host Cell DNA Sequences by Baculoviruses: Relationship between Host DNA Insertions and FP Mutants *Autographa califonica* and *Galleria mellonella* Nuclear Polyhedrosis Viruses. (1995) Virology 47, 287-300, attached.)

Furthermore, the system taught by Clark, can still replicate at low levels in normal insect cells. Therefore, the system suggested by Clark will produce baculovirus with mutations and will also produce baculovirus vectors containing foreign gene inserts which are contaminated by parental baculovirus without those inserts. In contrast, the system of the present invention does not replicate in normal insect cells. Accordingly, the present invention is not disclosed, taught or suggested

by Clark. Applicants respectfully assert that the rejection under 35 U.S.C. §102(e) has been overcome and request its withdrawal.

35 U.S.C. §103(a)

Claims 27-50 are rejected under 35 U.S.C. §103(a) as being unpatentable over Clark *et al.* (hereinafter Clark), in view of Nasmyth *et al.* (hereinafter Nasmyth). The Office Action states that one of ordinary skill in the art would be motivated to use the method of Nasmyth to clone the baculovirus of Clark for the expected benefit of reducing time consumption and reducing cost due to the lack of need for rounds of plaque purification and the ability to isolate multiple recombinants simultaneously. Applicants traverse this rejection.

Applicants assert that Clark discloses the use of a modified baculovirus that lacks a functional p-35 gene. (See Figure 2) The product of the p-35 gene allows the virus to replicate in Sf cells by preventing the cells from undergoing apoptosis. In the absence of p-35, the Sf cells undergo apoptosis and the virus cell cannot complete its replication cycle. In order to replicate the virus using the system described by Clark, a host cell such as *T. ni* must be used. In using this system, a heterogenous virus population is created prior to any experimentation, rendering the stock of virus unusable for repeat experimentation or as a control. (*See* Fraser, M.J. et al., Acquisition of Host Cell DNA Sequences by Baculoviruses: Relationship between Host DNA Insertions and FP Mutants *Autographa califonica* and *Galleria mellonella* Nuclear Polyhedrosis Viruses. (1995) Virology 47, 287-300, attached.)

Additionally, the system disclosed in Clark can still replicate at low levels in normal insect cells. This is in contrast to the present invention which cannot replicate in normal insect cells. In the system disclosed by Clark, there will always be some contaminating parental virus without foreign genetic material integrated into the virus. The relative levels of this parental virus can be reduced by, for example,

passaging several times through SF 9 host cells, but this requires extra work and can take several weeks to complete. The present invention does not require these additional steps.

The system disclosed by Clark therefore produces baculovirus with mutation as well as baculovirus vectors containing foreign gene inserts contaminated by parental baculovirus without those inserts.

Nasmyth is simply directed towards producing a recombinant baculovirus. The aim of Nasmyth is to use the yeast cell instead of insect cells to produce recombinant viruses. Applicants' invention allows the efficient production of vectors comprising foreign DNA. The use of the intermediate host allows the production of replication-deficient virus in high concentrations that are easily purified. No restriction enzyme digestion is required to produce the replication deficiency and the method produces sufficient replication deficiency to obviate the need for plaque assays to further purify the virus and remove any residual parental virus. This means that the claimed invention can be used for high throughput assays using the single step of applying the naked baculovirus at the same time as the foreign DNA to the cell. Further, the prior art does not allow for high throughput assays.

Additionally, the system disclosed by Nasmyth uses yeast that are not replication deficient to modify baculoviruses . In contrast, the present invention does not use the yeast cell to modify the baculovirus, but simply uses the yeast to allow the baculovirus vector to be replicated.

There is no teaching, motivation or suggestion to combine Clark with Nasmyth. Even if they were combined, they would not result in the present invention, as currently claimed. The aim of the Nasmyth paper is to use the yeast cell instead of insect cells to produce recombinant viruses. The present invention does not need to do this. The present invention replaces the insect cells for producing the baculovirus

vector prior to use. There is no teaching to combine the two separate techniques of Clark and Nasmyth. Accordingly, the present invention is not disclosed, taught or suggested by Clark in view of Nasmyth. Furthermore, there is no motivation to combine these references to derive Applicants invention as claimed. Applicants respectfully assert that the rejection under 35 U.S.C. §103(a) has been overcome and request its withdrawal.

35 U.S.C. §112, first paragraph

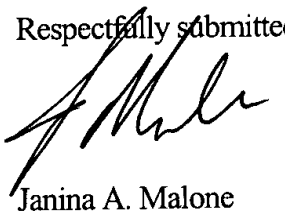
Claims 31-34 and 39-42 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants traverse this rejection.

The identification of functional fragments or mutations is a matter of routine experimentation, not undue experimentation. A person skilled in the art, if using a baculovirus that is not exemplified, would be able to identify functional genes in that baculovirus by following the same methods used to identify the functional genes in known baculoviruses. Once the functional gene is identified, a person skilled in the art would be able to readily identify functional fragments or mutations without undue experimentation. The separate genes recited in the claims indicate functional genes that are common within baculoviruses. For example, *dna pol* is ubiquitous, and would not be difficult to find, identify, fragment or mutate while still preserving a functional gene. Several other genes including *lef-2, lef-8* and *ie-1* are also found universally in baculoviruses. The assay for functionality is a simple one in that replication is either enabled or not enabled in the baculovirus. The identification of functional fragments does not involve undue experimentation. Accordingly, the claims of the present invention are described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the

application was filed, had possession of the claimed invention. Applicants respectfully assert that the rejection under 35 U.S.C. §112, second paragraph, has been overcome and request its withdrawal.

Applicants respectfully submit that this is a complete response to the Office Action dated December 18, 2002 and that Claims 27-50 are patentable. Early and favorable consideration is earnestly solicited. If the Examiner believes there are other issues that can be resolved by telephone interview, or that there are any informalities remaining in the application which may be corrected by Examiner's Amendment, a telephone call to the undersigned attorney at (404) 815-6500 is respectfully solicited.

Respectfully submitted,



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